TSCA HEALTH & SAFETY STUDY COVER SHEET

8EHQ-0601-14943S

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MR 48507

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1.0 SUBMISSION TYPE

8(d) **XX 8(e)** FYI 4 OTHER: Specify_____

XX- Initial Submission - Follow-up Submission Final Report Submission

Previous EPA Submission Number or Title if update or follow-up: Docket Number, if any: #

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2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e): optional for §4, 8(d) & FYI) X- YES NO	**2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID** 7106 4575 1292 03377852 01-2-7	**2.3 FOR EPA USE ONLY**

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY

Reported Chemical Name (specify nomenclature if other than CAS name):

CAS# N/A

Purity ___%

X- Single Ingredient

Commercial/Tech Grade

Mixture *Trade Name:* BYI 08330 *Common Name*: tetramic acid

	CAS Number	*NAME*	*% WEIGHT*
Other chemical(s) present In tested mixture			

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4.0 REPORT/STUDY TITLE

Dose Range Findings Study for Future Guideline Study

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5.1 STUDY/TSCATS INDEXING TERMS

[CHECK ONE]

HEALTH EFFECTS (HE):__X___ ENVIRONMENTAL EFFECTS (EE):_____ ENVIRONMENTAL FATE (EF):___

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)

STUDY TYPE:	SUBJECT	ROUTE OF	VEHICLE OF
	ORGANISM (HE, EE only) RATS	EXPOSURE (HE only):__	EXPOSURE (HE only)_
Other:Dose Range Finding		*Other:*	*Other:*

6.0 REPORT/STUDY INFORMATION Study is GLP

Laboratory Bayer Toxicology Report/Study Date_5/25/01

Source of Data/Study Sponsor (if different than submitter) _____Number of pages _-

continuation sheet attached

7.0 SUBMITTER INFORMATION

Donald W. Lamb
VP, Product Safety & Regulatory Affairs Phone: 412-777-7431
Bayer Corporation - 100 Bayer Road, Pittsburgh, PA. 15205

Submitter Address (if different): _____
Technical Contact: ___Same as above_____ Phone: ( )_____

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8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS

This compound is

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Submitter Signature: Donald W Lamb **Date: 5/25/01**

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Continuation of 2.1

In this study, the incidence of common malformations was possibly increased at the 1000 mg/kg dose level together with reduced fetal weights, retarded ossification, and an increase in the incidence of skeletal variations (wavy ribs and 14th ribs). At the 800 mg/kg dose level, retarded ossification and an increased incidence of wavy ribs were observed. Thus the reporting.

Summary Seven inseminated female Wistar rats per group (200 mg/kg group: 11 and 1000 mg/kg group: 8) were treated by gavage from days 6 to day 19 p.c. with doses of 0, 50, 200, 800, and 1000 mg/kg of BYI 08330 in 0.5% aqueous carboxymethylcellulose (dose volume of 10 ml/kg). For better clarification of toxic effects, 7 further females were added later on to the 1000 mg/kg dose group. The fetuses were delivered by cesarean section on day 20 p.c. Investigations were performed on the general tolerance of the test compound by the females as well as on its effect on intrauterine development.

Treatment related effects on respiration (transiently gasping, labored breathing, and respiratory sounds), water intake (increased/decreased water intake at the end of treatment), excretion (increased urination and light colored feces) and appearance (piloerection) were restricted to the 1000 mg/kg group. Slight body weight loss for one day (6 to 7 p.c.) occurred at a dose level of 800 and 1000 mg/kg; in the 1000 mg/kg group together with slightly reduced feed intake during treatment and a more pronounced reduction at the end of treatment. Reduced carcass weight and corrected body weight gain were observed at the 800 mg/kg level (marginal effects) and to a more distinct degree in the 1000 mg/kg group. Final body weight and body weight gain during gestation were also distinctly reduced in the 1000 mg/kg group. Necropsy revealed no treatment-related findings at a dose level up to 800 mg/kg and toxicological relevance was not assumed for slight renal pelvis dilation seen in one female in the 1000 mg/kg group, due to comparable findings in historical controls.

Reproductive parameters, i.e. gestation rate, postimplantation loss, litter size and fetal sex distribution were not affected to a toxicologically relevant degree by treatment at a dose level up to and including 1000 mg/kg. A marginal reduction of placental weight was seen at a dose level of 800 and 1000 mg/kg; in the 1000 mg/kg group an increased incidence of necrotic placental borders and possibly engorged placentae were also observed. A marginal effect on fetal weight (reduction) could not be completely excluded at dose levels of 200 and 800 mg/kg and was clearly evident at the 1000 mg/kg dose level. Final evaluation of this finding at the 200 mg/kg and 800 mg/kg dose levels was not possible in this pilot study.

The overall incidence of common unspecific malformations (dysplastic tubular bones and interatrial septal defect of the heart) was marginally increased at the distinctly maternal toxic 1000 mg/kg dose level (i.e. 5.5% of fetuses and 35.7% of litters affected), though these findings were within the upper range of historical control data. One case each of dysplastic tubular bones was seen in the other dose groups; at the 800 mg/kg dose level together with one case of interatrial septal defect. Since these malformations are common findings in the rat strain used and the incidence was within the range of historical control data, toxicological relevance was not assumed for these findings up to and including the 800 mg/kg dose level. Final evaluation was not possible at the 1000 mg/kg level in this pilot study.

Continuation

External and visceral fetal evaluation gave no further indication for toxicologically relevant effects up to and including 1000 mg/kg.

Retarded fetal ossification together with a marginal to slight increase in the incidence of wavy ribs (variation) occurred at a dose level of 800 and 1000 mg/kg. The incidence of additional 14th ribs (variation) was slightly increased at the 1000 mg/kg level.

In summary, maternal effects were seen at the 800 mg/kg dose level (body weight loss and impaired body weight development) and were distinct at the 1000 mg/kg dose level (respiratory findings, piloerection, body weight loss, impaired body weight gain, increased/decreased water intake, increased urination, and light colored feces). Effects on intrauterine development could not be completely excluded at the 200 mg/kg level (possible marginally reduced fetal weight), were evident at a dose level of 800 mg/kg (reduced placental and possible fetal weight, retarded ossification, and wavy ribs) and were clearly observed at the 1000 mg/kg dose level (distinctly reduced fetal and placental weight, necrotic placental borders, retarded ossification, wavy and 14th ribs, and a possible marginal increased incidence of common malformations).